Environmental Perchlorate Exposure and Human Health: from Newborn to Cancer

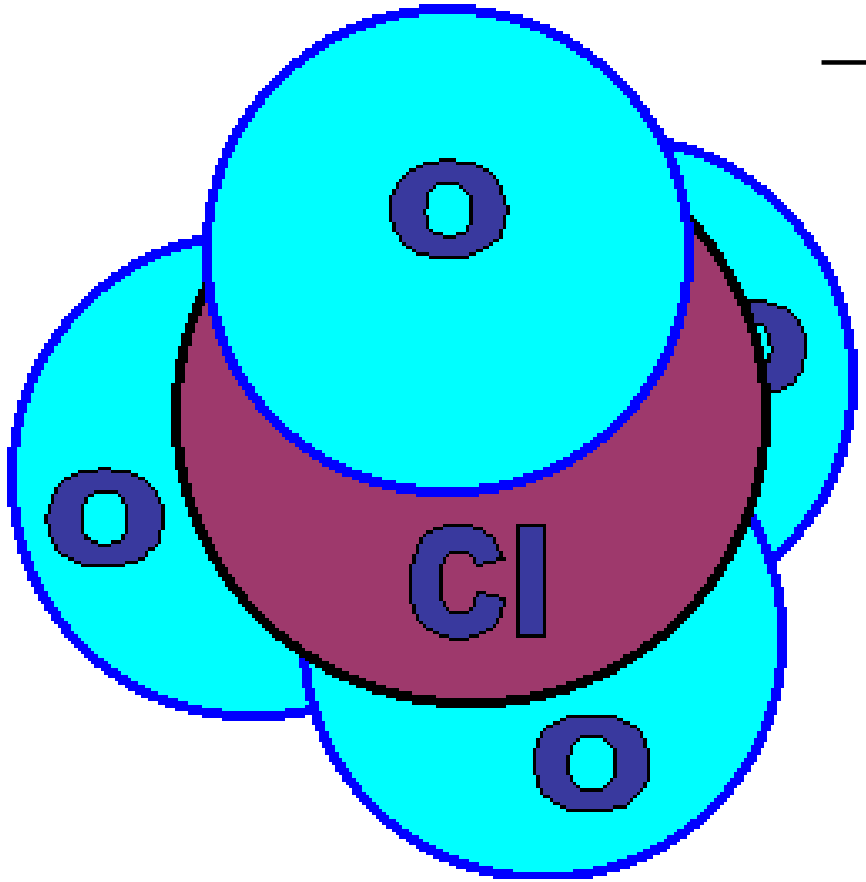
Steven H. Lamm, MD, DTPH

Department of Pediatrics
Georgetown University Medical Center
and
Consultants in Epidemiology
& Occupational Health, Inc.
Steve@CEOH.com

August 23, 2000

Structure of Perchlorate

ClO_4^-



Perchlorate

Medical

Hyperthyroidism Treatment
Hyperthyroidism of Pregnancy
Amiodarone toxicity
Perchlorate discharge test

Industrial

Explosives, Fertilizer
Fireworks - propellant
Accelerant -
* Atlas Missile
Space Station

Occupational and Environmental Concerns

Effect of Perchlorate on the Human Thyroid Gland

By JOHN B. STANBURY AND JAMES B. WYNGAARDEN

A FUNDAMENTAL property of the thyroid gland is that of removing iodide from the perfusing blood and concentrating it in the processes of hormone synthesis and storage. During recent years a large number of substances have been found that interfere specifically with either iodide capture (trapping) or hormone synthesis. Among those preventing the latter are clinically important drugs such as propylthiouracil and 1-methyl-2-mercaptoimidazole. These prevent the oxidation of iodide ion to iodine and its chemical attachment to tyrosyl groups. It remains in doubt whether this occurs through inhibition of an oxidative enzyme, or from maintenance of the trapped iodide ion in the reduced state, or through some other mechanism. It is evident, however, that thiourea and related substances do not prevent the *trapping* of iodide by the gland.[1]

From the Thyroid Clinic of the Massachusetts General Hospital, Boston.

Supported in part by grants from Parke-Davis and Co., Detroit, Mich., the Atomic Energy Commission, and the American Cancer Society, an institutional grant to the Massachusetts General Hospital from the American Cancer Society, and the H.N.C. grant to Harvard University.

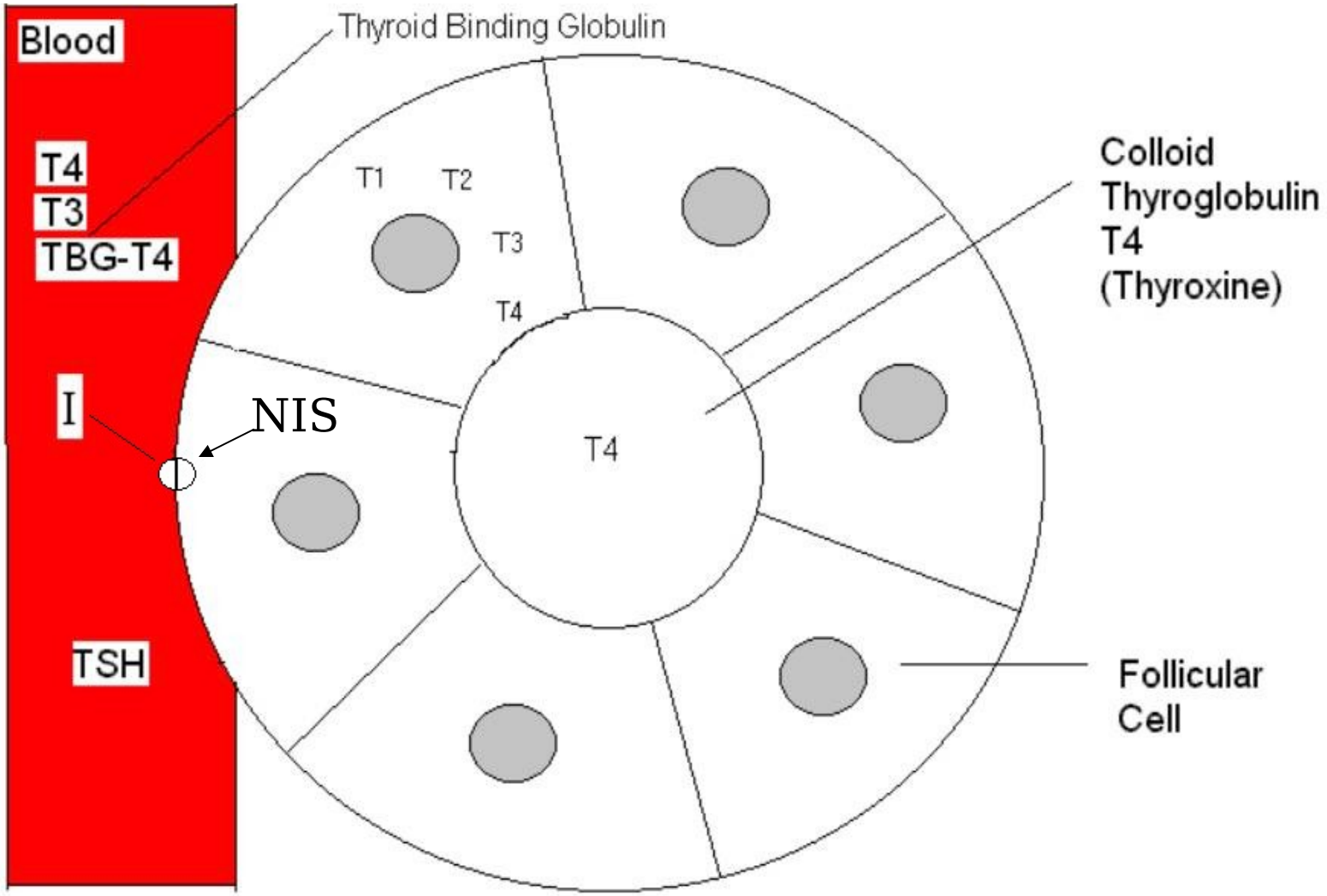
Received for publication July 5, 1952.

Hofmeister Series

(Group VII in the Periodic Table)
in order of decreasing potency

Technetate	TcO_4^-
Rhenate	RnO_4^-
Perchlorate	ClO_4^-
Thiocyanate	SCN^-
[Iodide]	I^-
Nitrate	NO_3^-
Bromide	Br^-
Chloride	Cl^-

T_4 (Thyroxine) Synthesis



History of Perchlorate's Clinical Use

- 1952-1965 Treatment of Grave's Disease

  200 mg TID to 600 mg TID

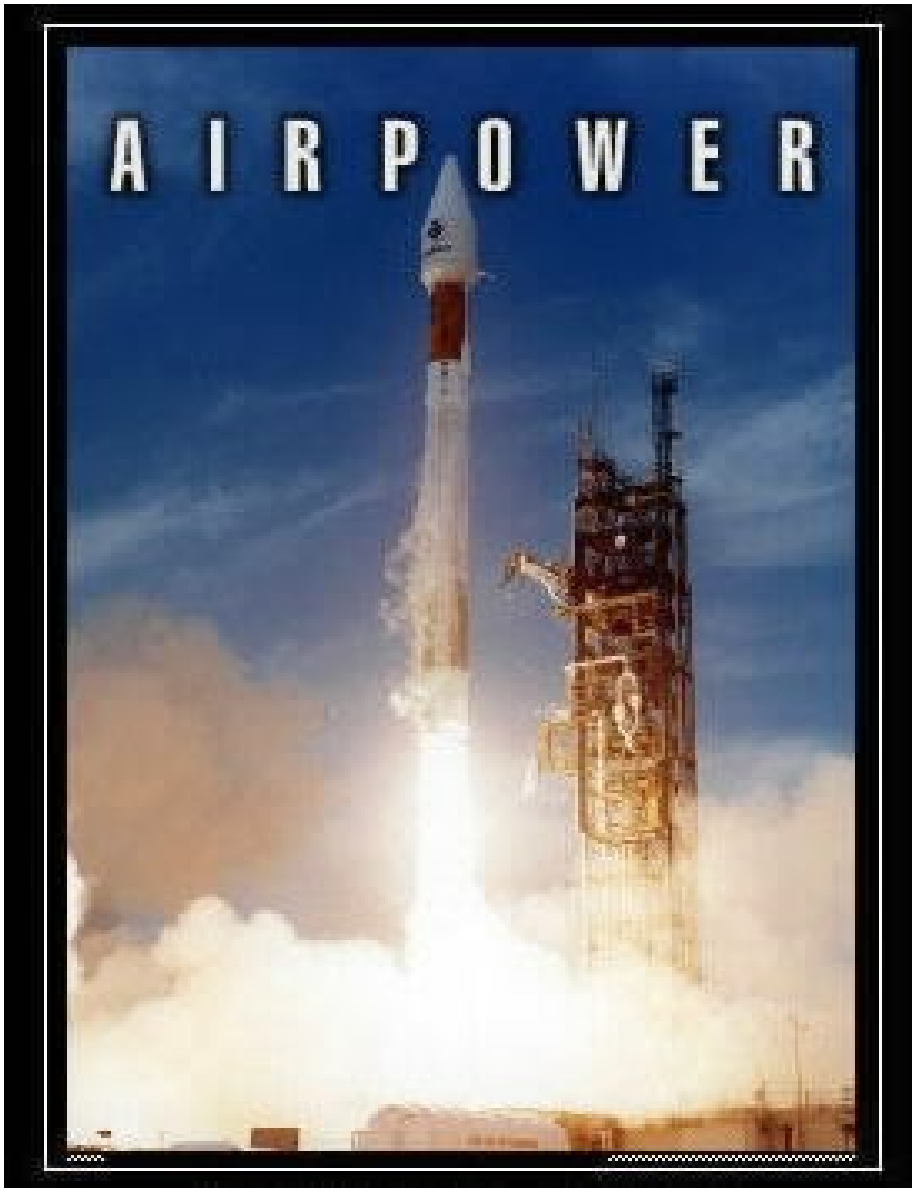
- 1960-1965 Case reports of agranulocytosis and of aplastic anemia at 1,000 mg/day (+)

- 1980-current Treatment for amiodarone toxicity

  900 mg/day initiation

  100 mg/day maintenance

Industrial Use



US Map Showing Perchlorate Sites in Southwest

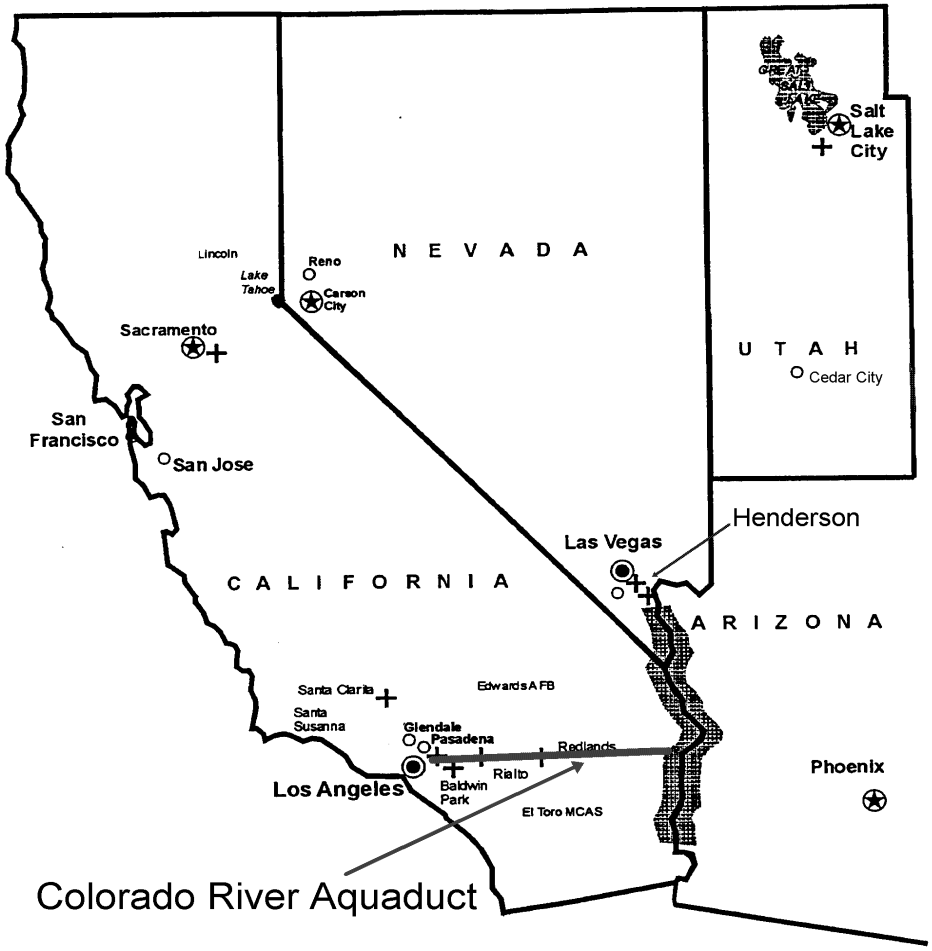
Environmental Contamination by Perchlorate

- CDHS 1985 study at a Sacramento aerospace site was rejected by CDC as the assay was only sensitive to 0.4 ppm ClO_4^-.
- CDHS in April 1997 reported a more sensitive assay at 0.004 ppm (or 4 ppb) ClO_4^-.
- Sacramento contamination level was found to be 0.3 ppm or 300 ppb.
- Southern California waters found to be at 5 – 8 ppb ClO_4^- or 0.01-0.16 mg/day.

Why the contamination?

Is it important?

Map of Southern California Water Distribution

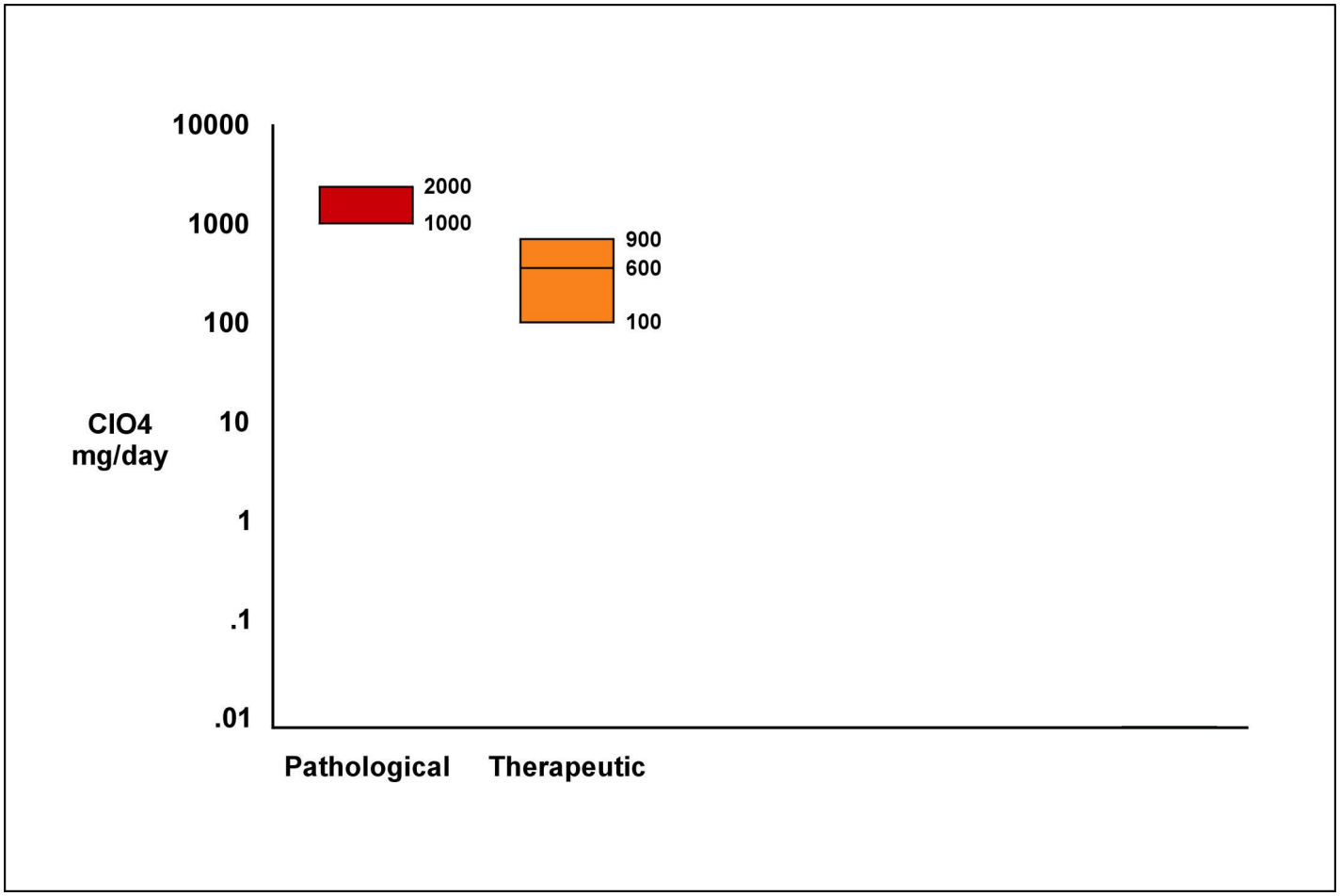


Known Human Health Effects of Perchlorate

- Known Toxicity:
  - Bone marrow effects occur at 1000 (+) mg/day.
  - Transient neonatal goiter seen at 600 mg/day.
- Treatment Dosages:
  - Initiation dose at 900 mg/day
  - Predominant dose of 600 mg/day
  - Maintenance dose at 100 mg/day

Note: Animal studies essentially show no non-thyroidal perchlorate effect.

Pathologic and Therapeutic Exposure Ranges (mg/day)



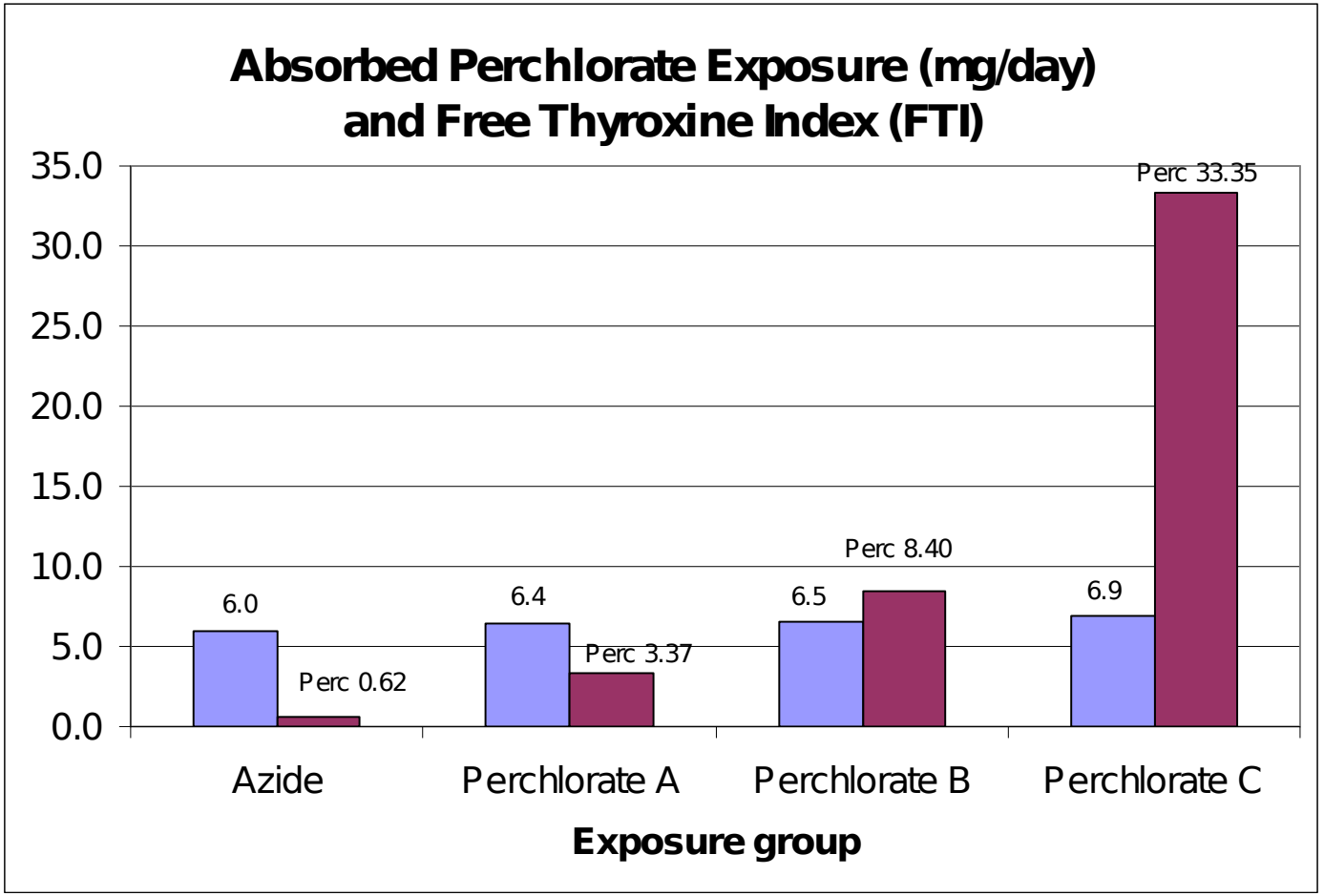
Unknown Health Effects of Perchlorate

- Effect on workers at occupational levels? What are the occupational levels?
- Effect on neonate, children, and adults at Environmental levels?
- Increased risk of thyroid cancer at Environmental levels?

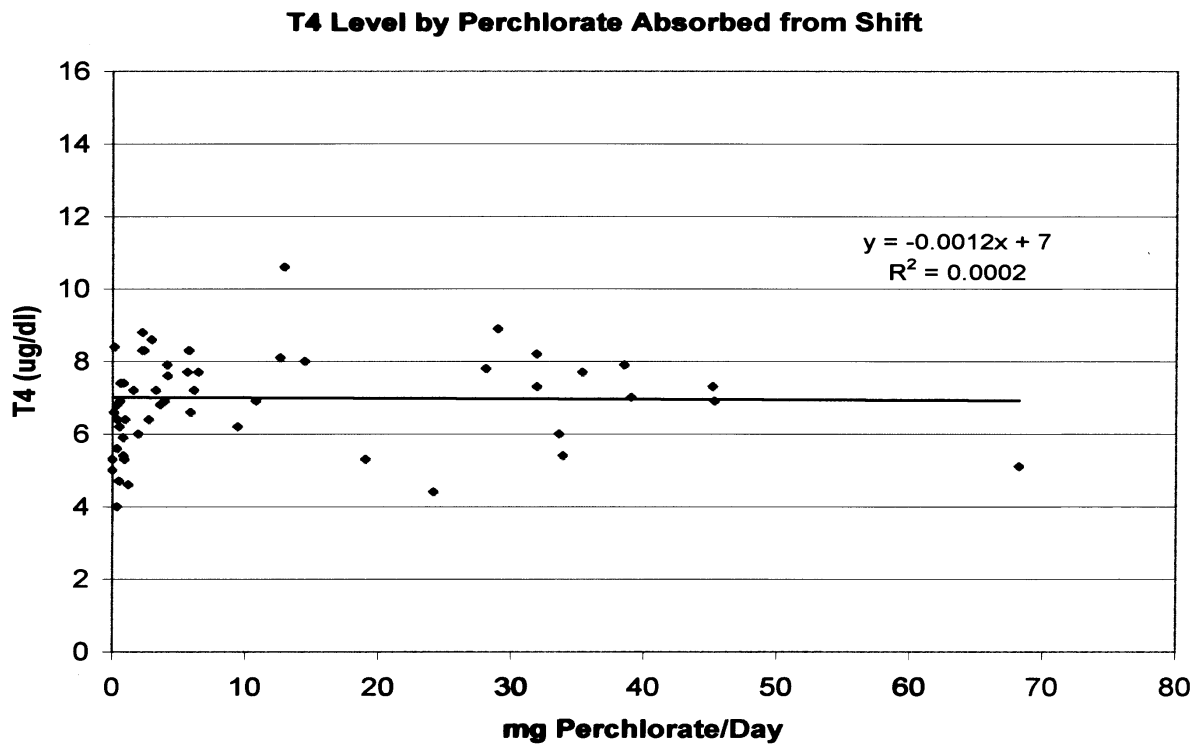
Occupational Study

Group	Absorbed Dosage *mg/day*	Serum Perchlorate *ppm*	TSH (med) *uU/ml*	FTI (med)
High	33.4	1.60	2.8	6.9
Medium	8.4	0.41	2.2	6.5
Low	3.4	0.11	2.5	6.4
Comparison	0.6	0.00	2.8	6.0

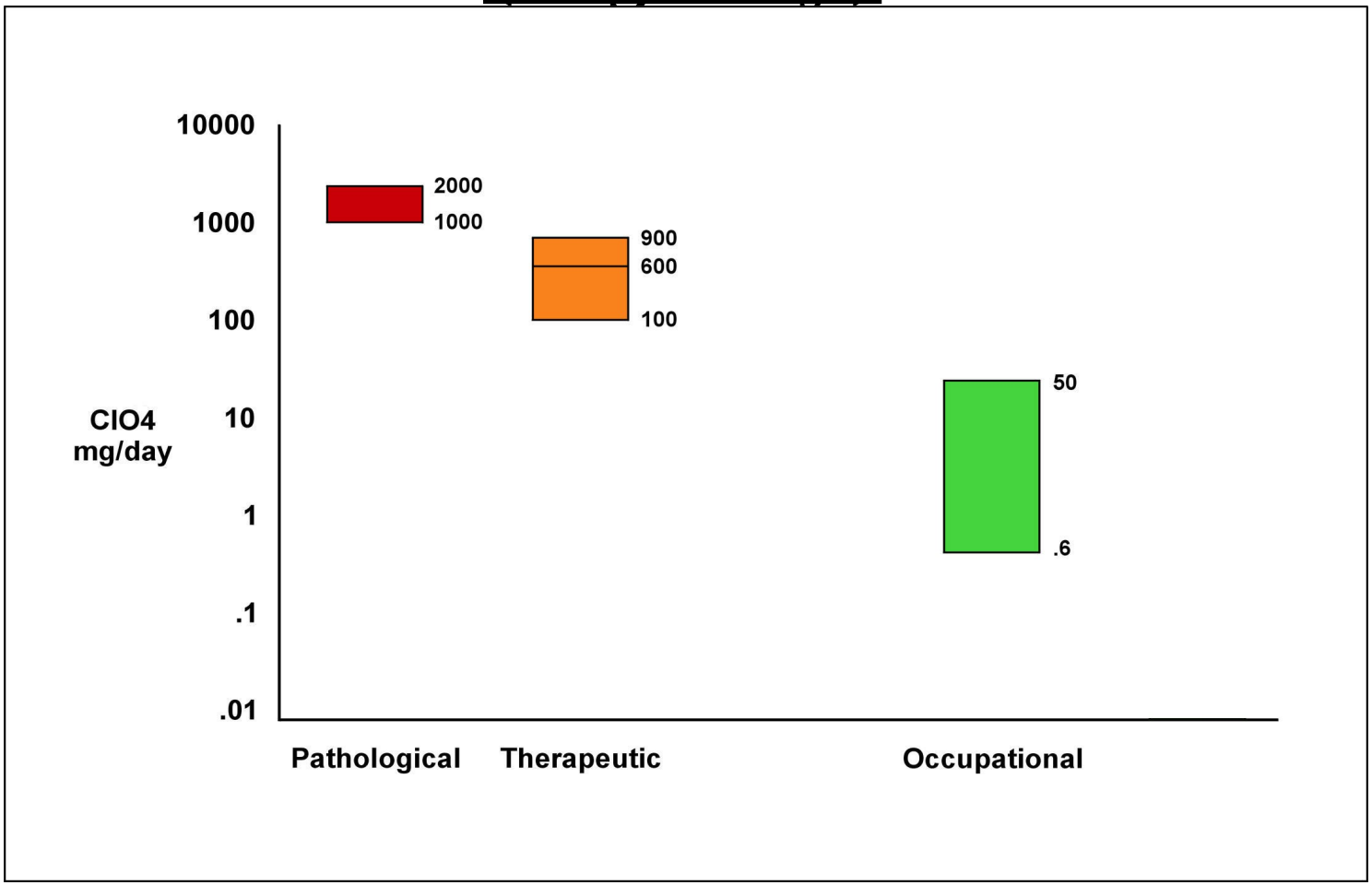
Occupational Study Results Hormone Level vs Exposure



Occupational Study Results Hormone (T_4) Level vs Exposure



Pathologic, Therapeutic, and Occupational Exposure Ranges (mg/day)



Environmental Exposures

Location	Concentration (ppb = ug/l)
• California	5 – 8
• Nevada	5 – 16
• Chile	<4 – 120

Pediatric Outcomes

Congenital Hypothyroidism
Transient Neonatal Hypothyroidism
Pediatric Hypothyroidism
Pediatric Goiter

Adult Outcomes

Acquired Hypothyroidism
Thyroid Disease
Thyroid Cancer

Counties in California and Nevada with Perchlorate in Drinking Water

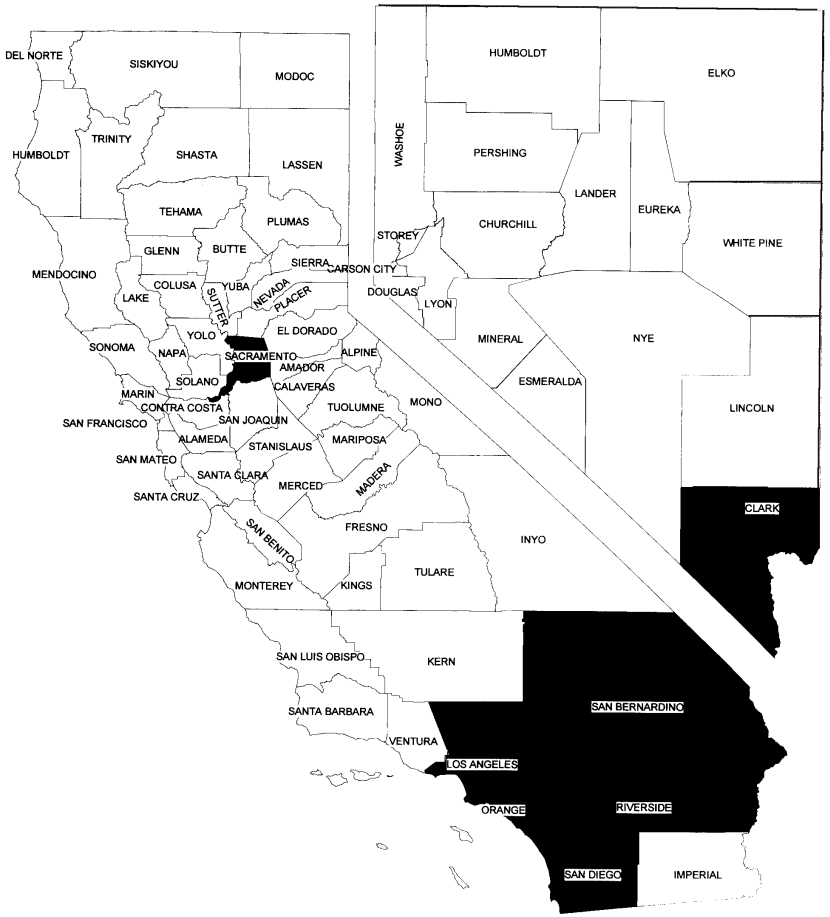


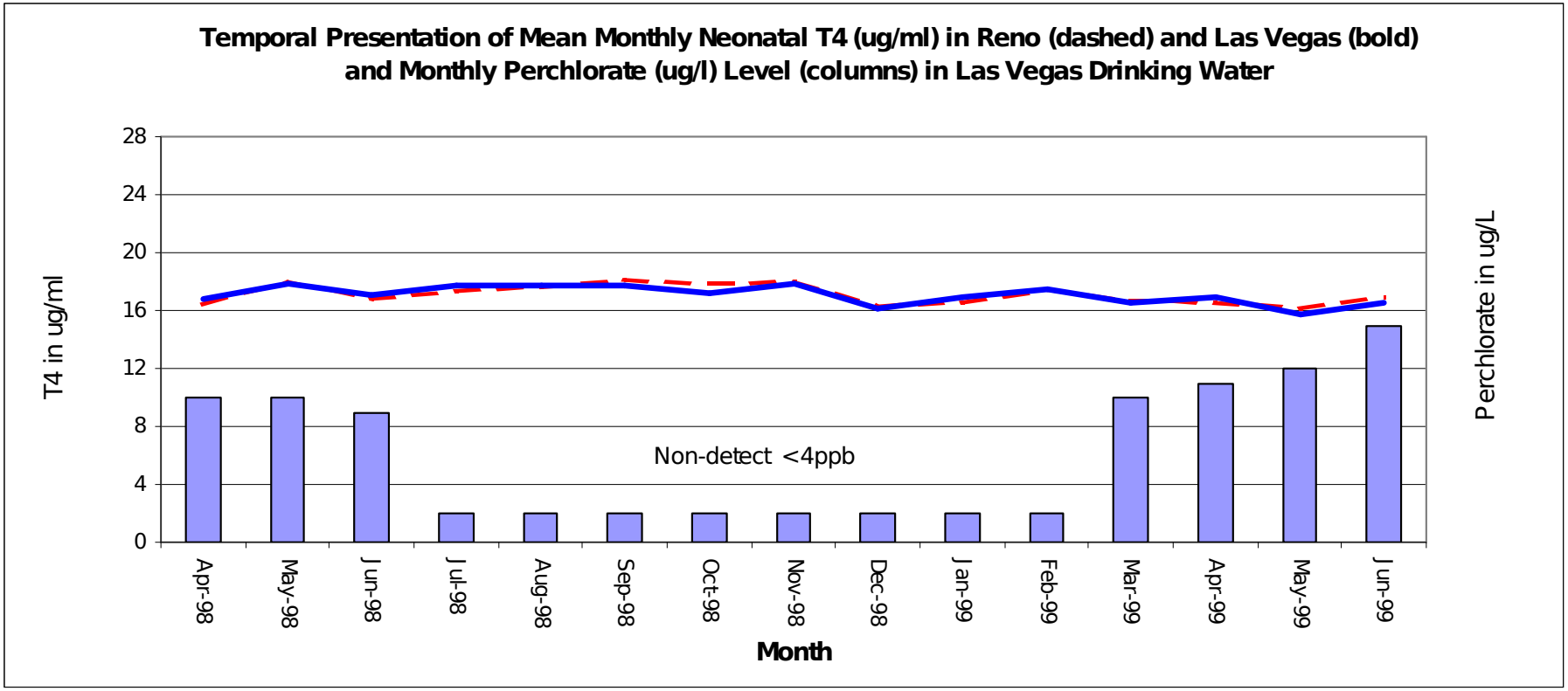
Fig. 1. Counties in California and Nevada with perchlorate detected in drinking water.

Congenital Hypothyroidism in California and Nevada

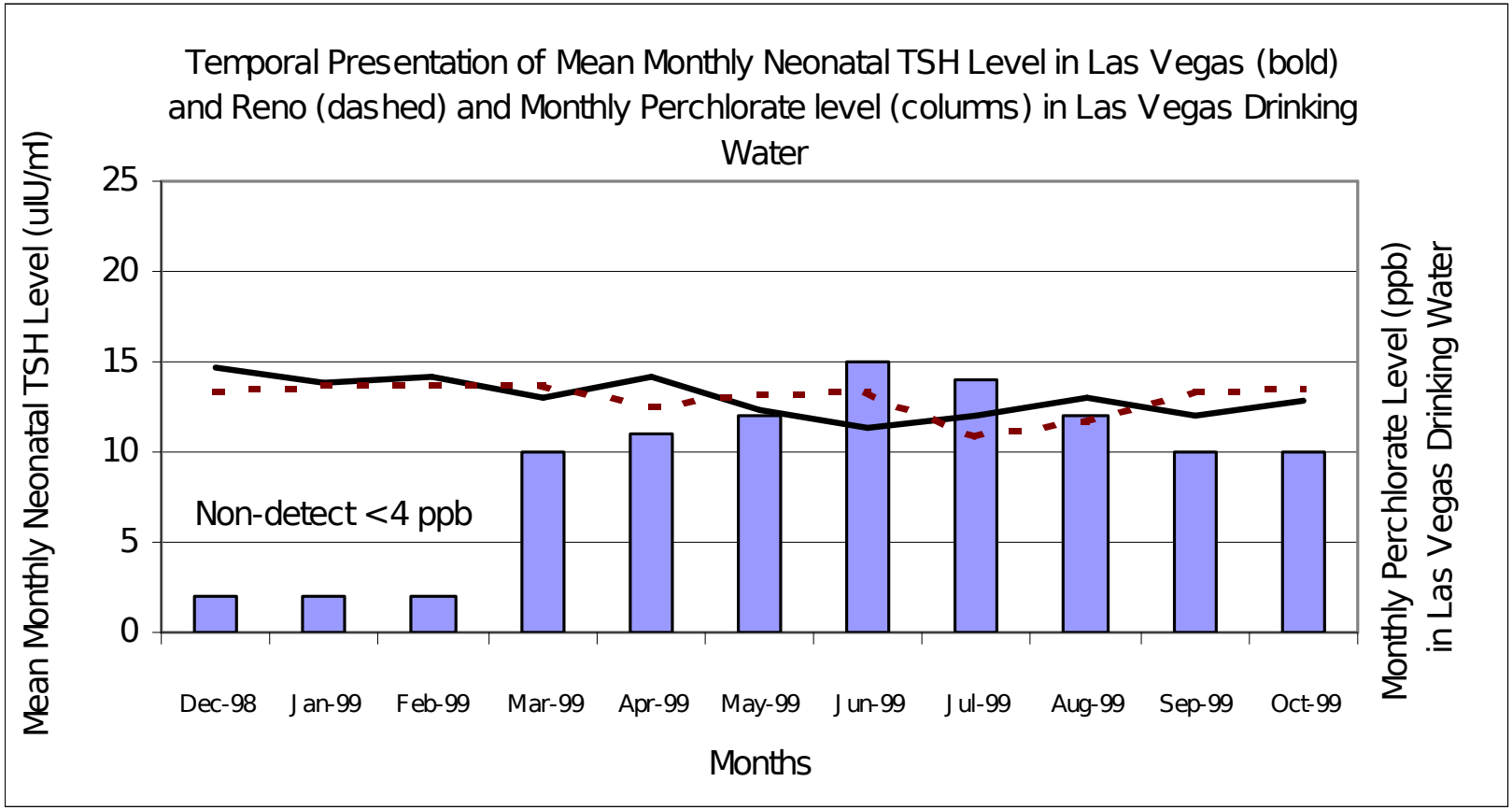
State/County	Newborns (number screened)	Congenital Hypothyroidism Cases		Ratio of Observed/ Expected	95% Confidence Limits
		Observed	Expected		
Nevada					
Clark	36,016	7	8.3	0.8	0.34 to 1.74
California					
Los Angeles	338,934	136	123.5	1.1	0.92 to 1.30
Orange	101,227	40	35.9	1.1	0.80 to 1.52
Riverside	43,577	11	15.6	0.7	0.35 to 1.26
Sacramento	39,235	8	12.9	0.6	0.27 to 1.22
San Bernardino	51,637	17	18.4	0.9	0.54 to 1.48
San Diego	80,582	30	28.2	1.1	0.72 to 1.52
Total	655,192	242	234.6	1.0	0.90 to 1.16
All seven counties	691,208	249	242.9	1.0	0.90 to 1.16

* Expected numbers have been adjusted for Hispanic ethnicity.

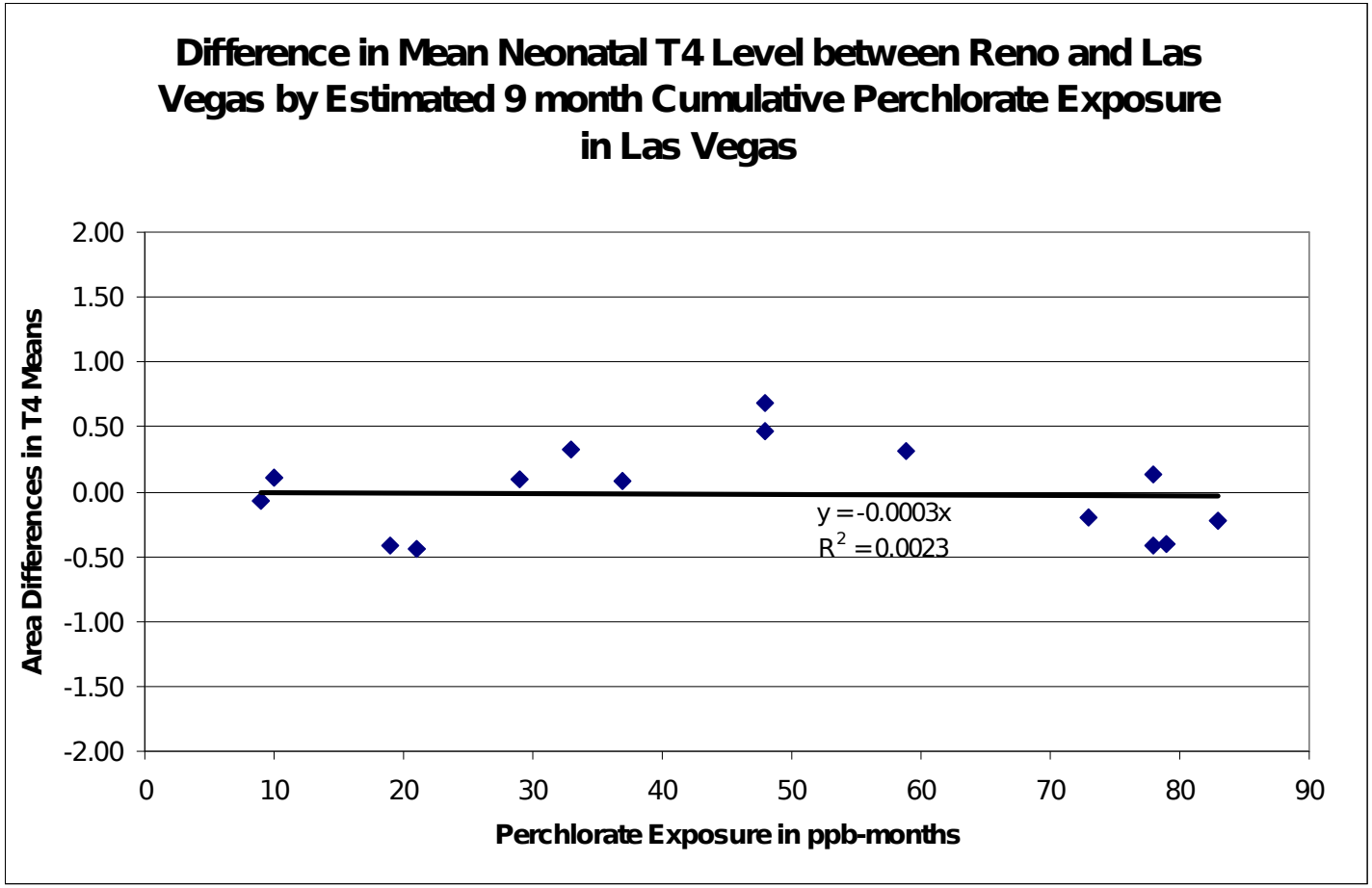
Transient Neonatal (T_4) Hypothyroidism in Nevada



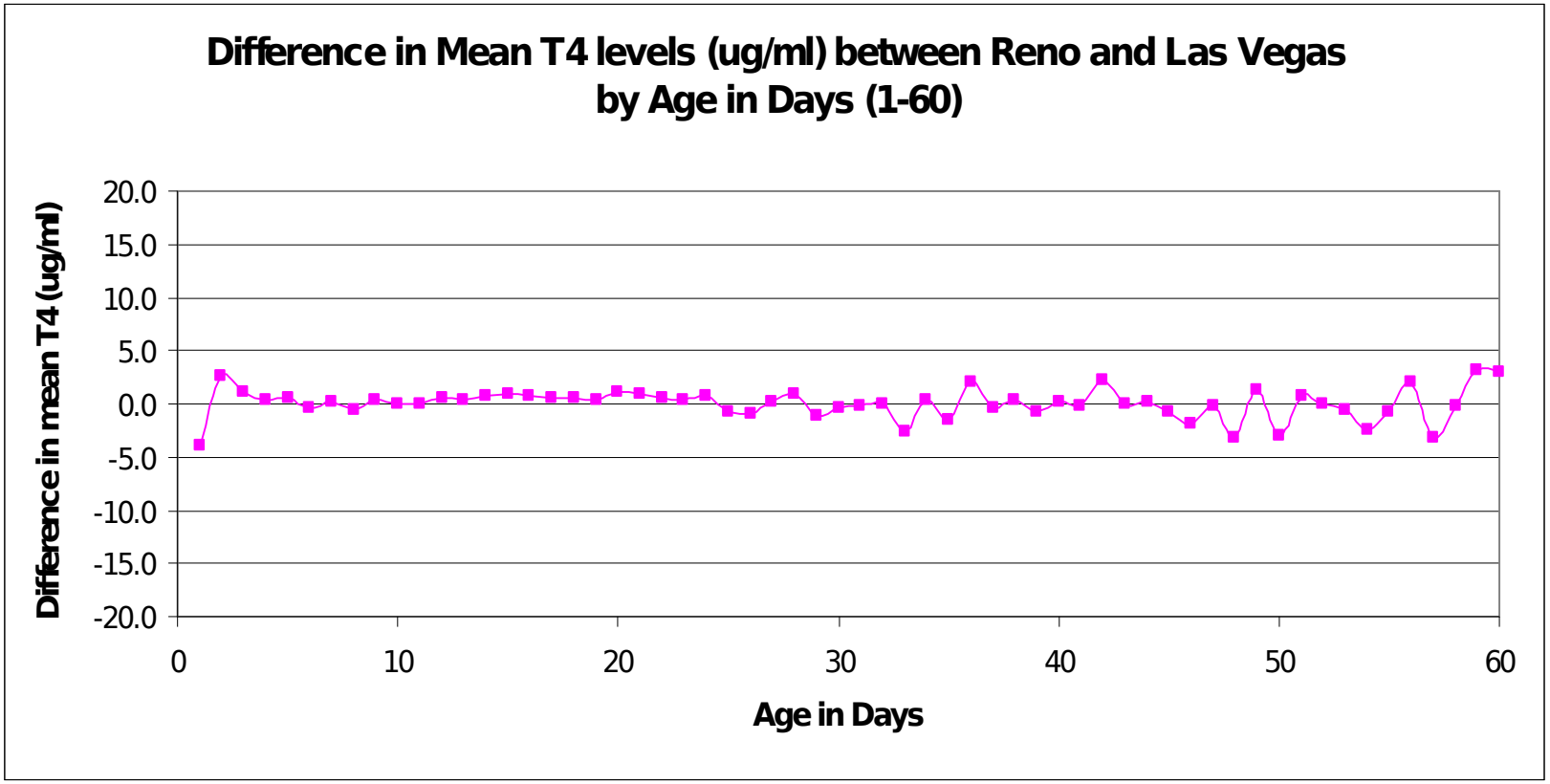
Transient Neonatal (TSH) Hypothyroidism in Nevada



Transient Neonatal (T_4) Hypothyroidism by Dosage



Transient Neonatal (T_4) Hypothyroidism by Age (days)



Transient Neonatal (TSH) Hypothyroidism in Chile

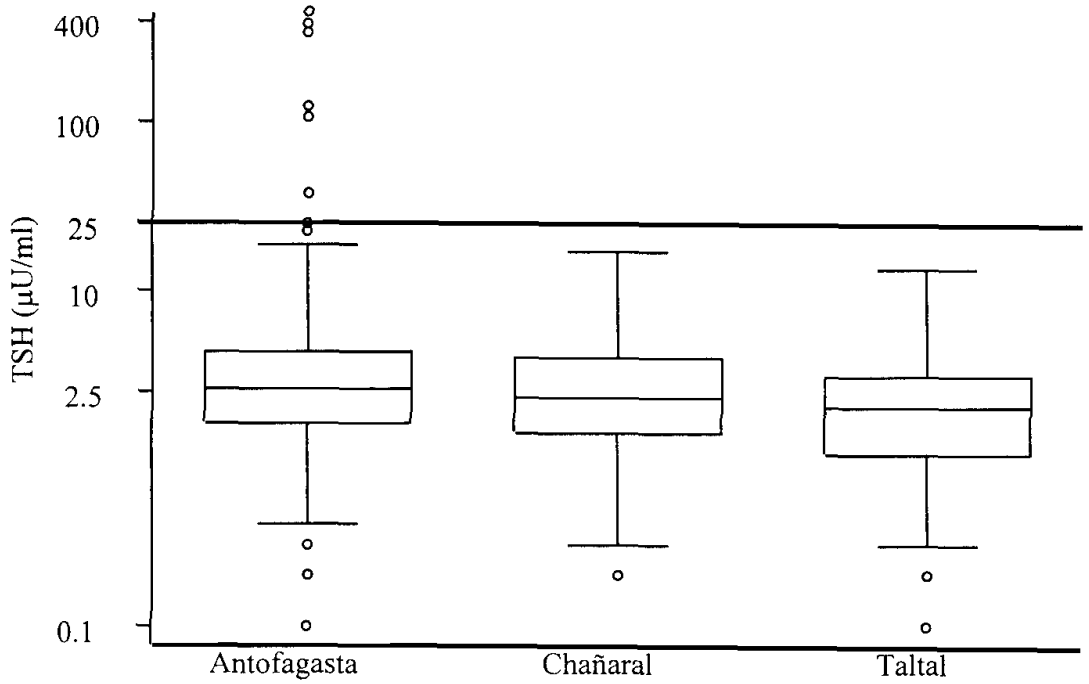


Fig. 2. Neonatal TSH (μU/mL) distribution in select cities in Chile, plotted on natural logarithmic scale. Center lines of boxes represent medians; upper and lower borders of boxes represent the 75th and 25th percentiles, respectively.

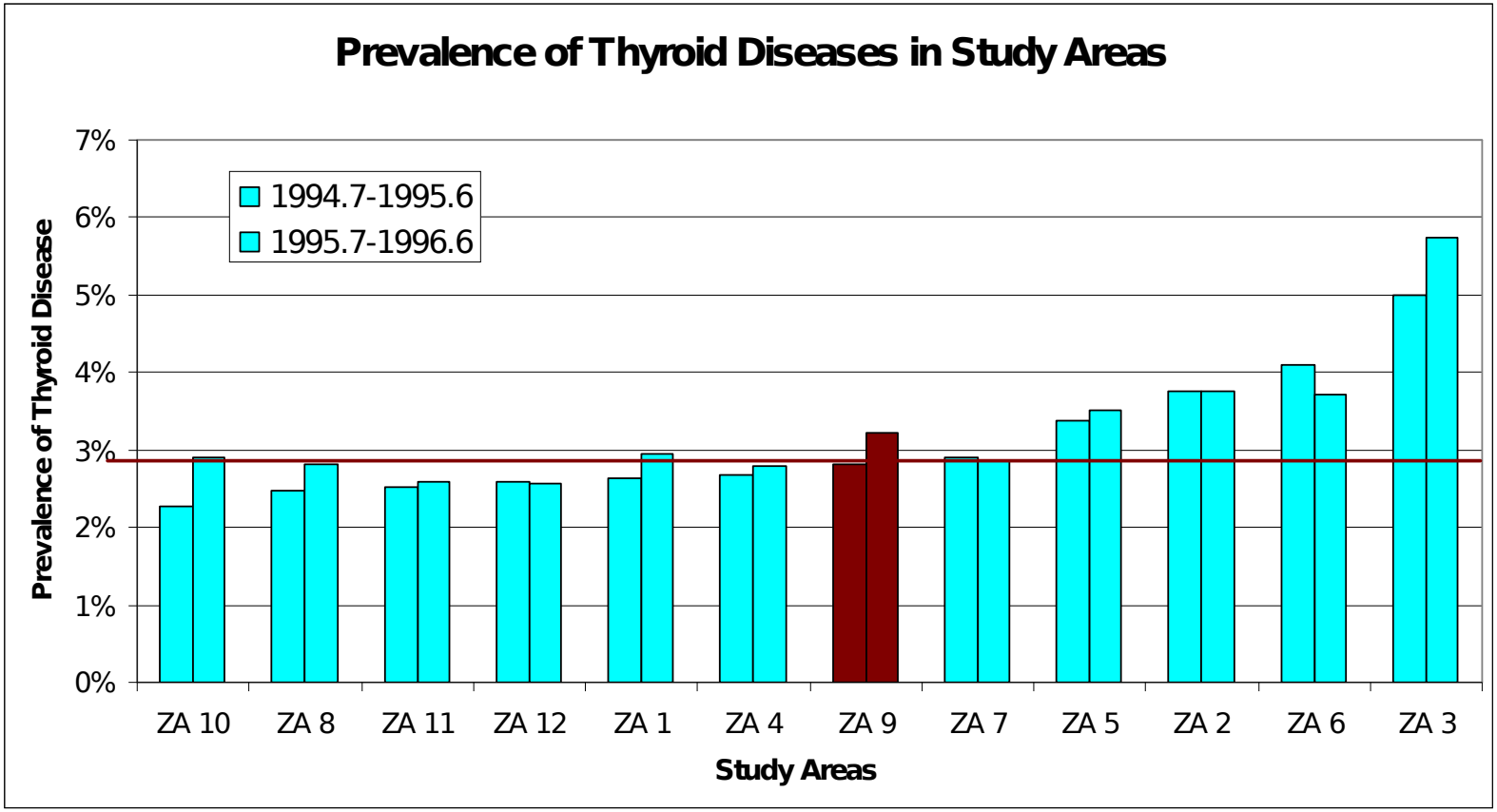
Pediatric Hypothyroidism in Chile

(School-aged 6-8 year/olds)

	Antagosta	Chanaral	Tatal
Number	(n=53)	(n=49)	(n=60)
Exposure	**<4 ppb**	**5 – 7 ppb**	**100 – 120 ppb**
TSH (uU/ml)	3.3 +/- 1.8	2.9 +/- 1.3	3.0 +/- 1.4
T4 (ug/dl)	9.1 +/- 1.3	10.4 +/- 1.4	9.3 +/- 1.2
FTI	1.2 +/- 0.1	1.3 +/- 0.1	1.4 +/- 0.2
Goiter	17.0 %	26.5 %	23.3 %

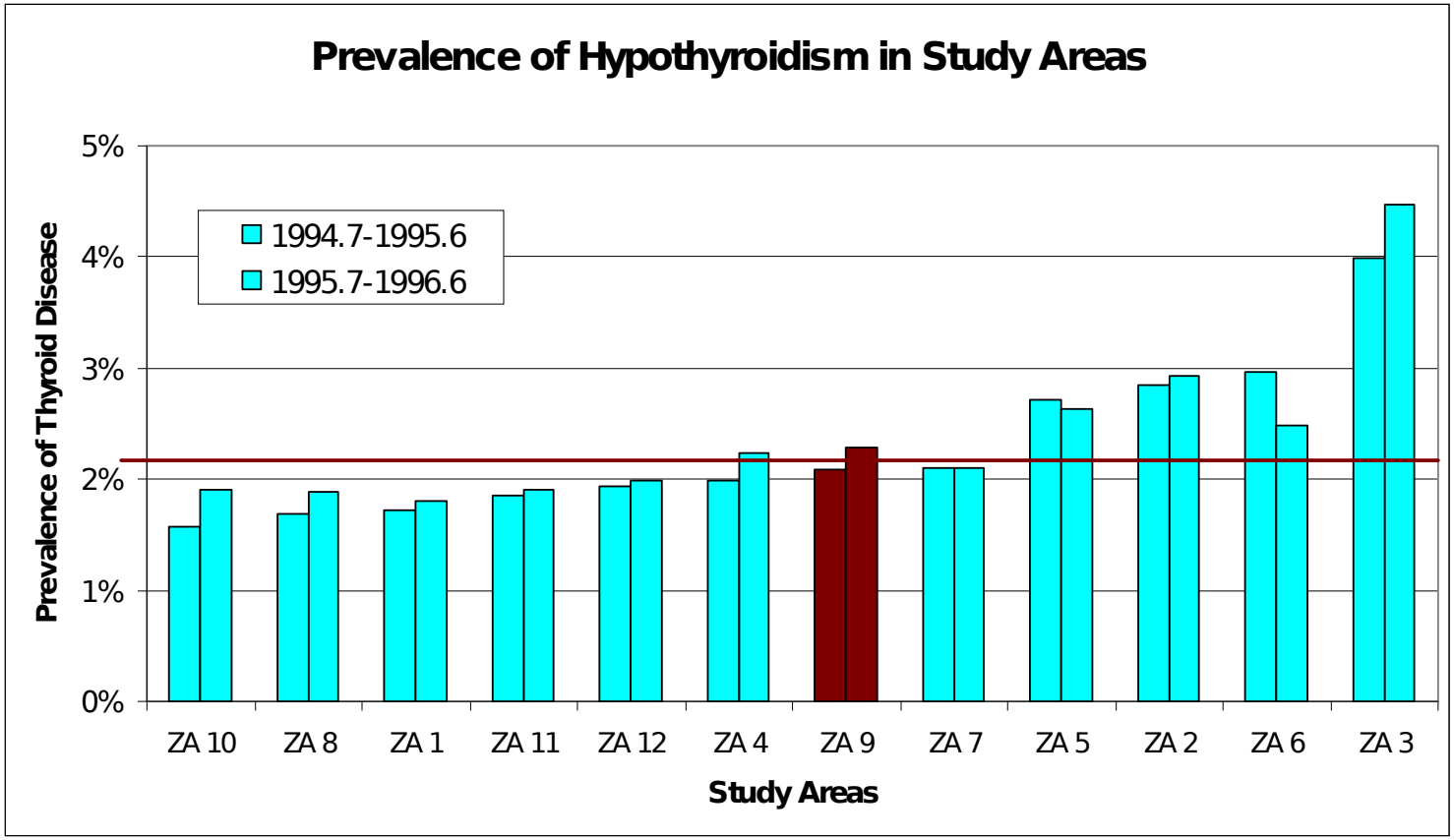
Adult Thyroid Disease

Medical data from demographically similar areas

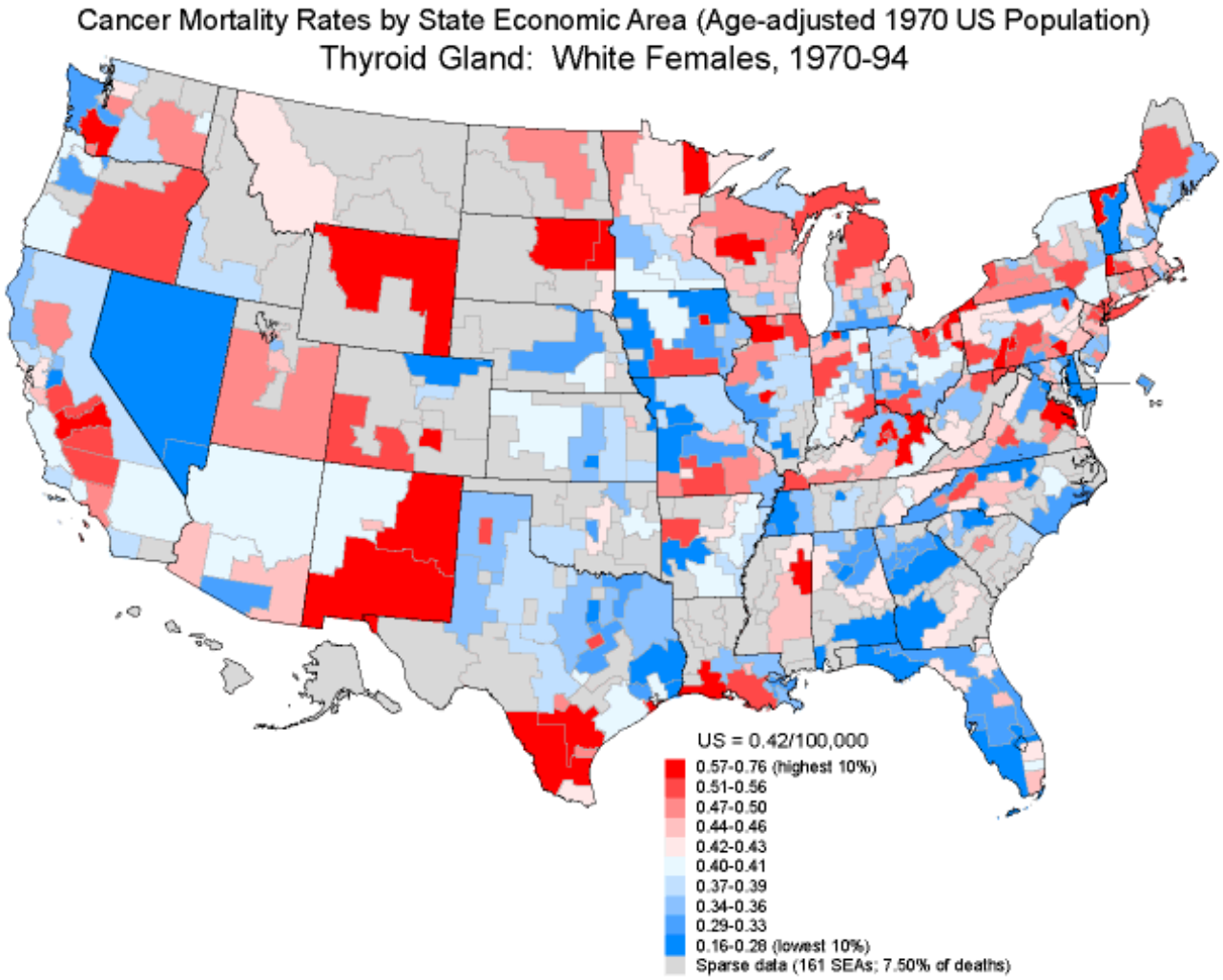


Adult Hypothyroid Disease

Medical data from demographically similar areas

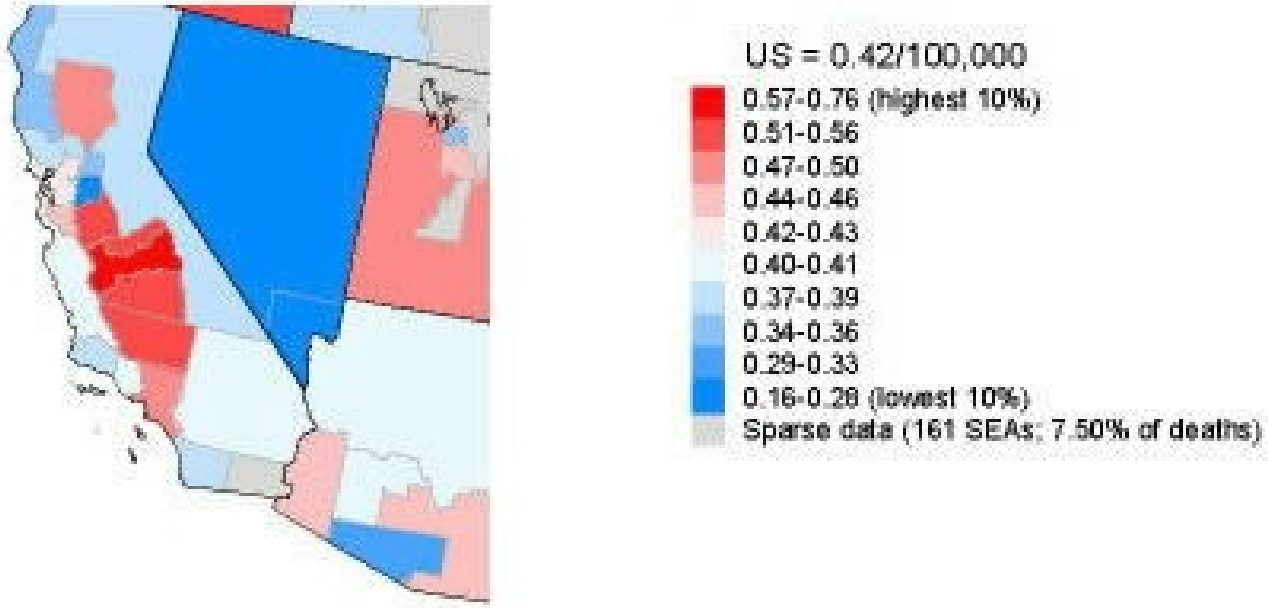


Thyroid Cancer



Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)

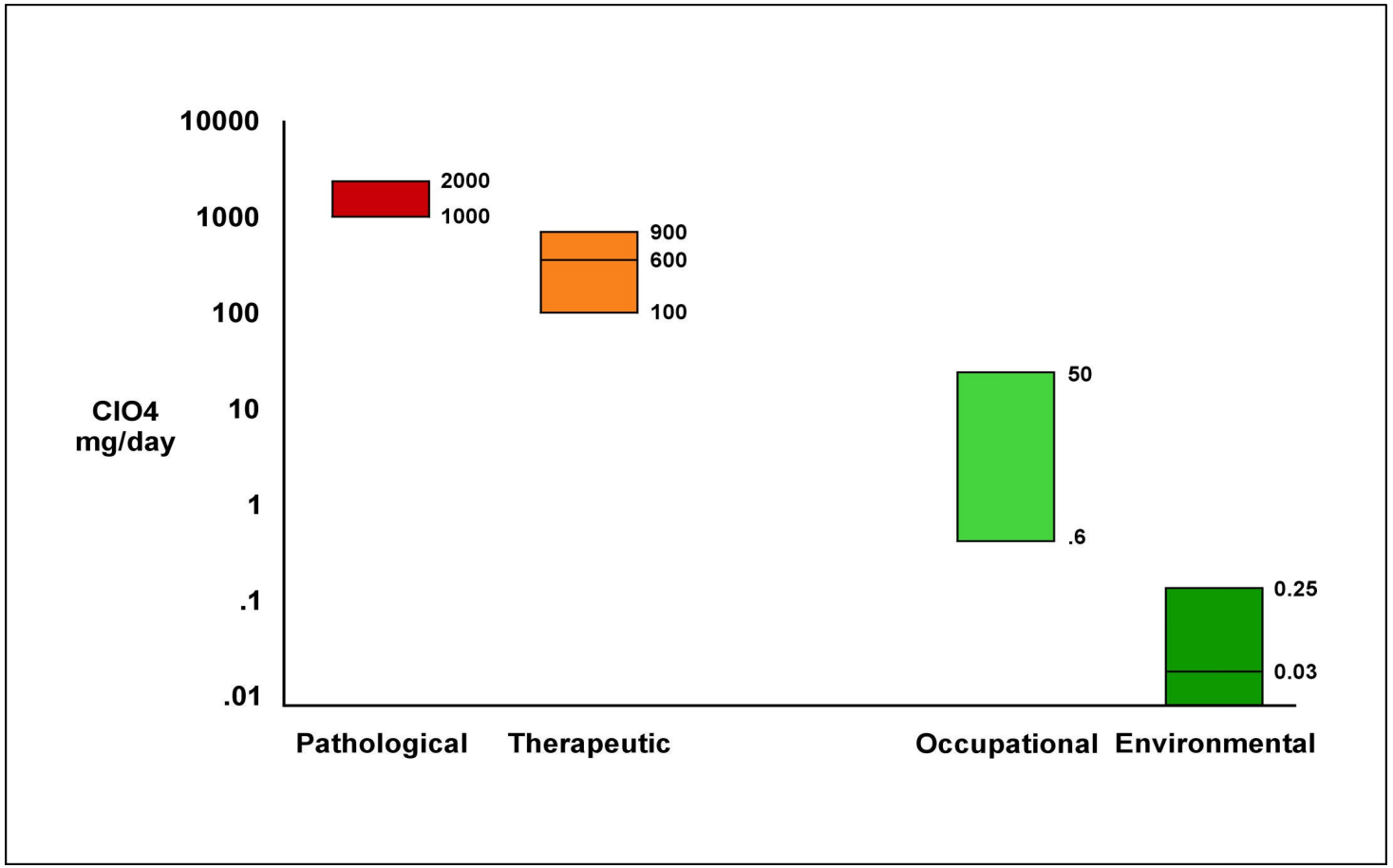
Thyroid Gland: White Females, 1970-94



The Thyroid and Environmental Perchlorate Exposure

	Outcomes
Pediatric	
Congenital Hypothyroidism	No
Transient Neonatal Hypothyroidism	No
Pediatric Hypothyroidism	No
Pediatric Goiter	No
Adult	
Acquired Hypothyroidism	No
Thyroid Disease	No
Thyroid Cancer	No

Pathologic, Therapeutic, Occupational and Environmental Exposure Ranges (mg/day)



Why do we find “safe” levels?

Pharmacology of Perchlorate

Perchlorate acts by inhibiting thyroidal uptake of iodine,

but at what exposure level?

Laboratory Exposure Study of Perchlorate in Water

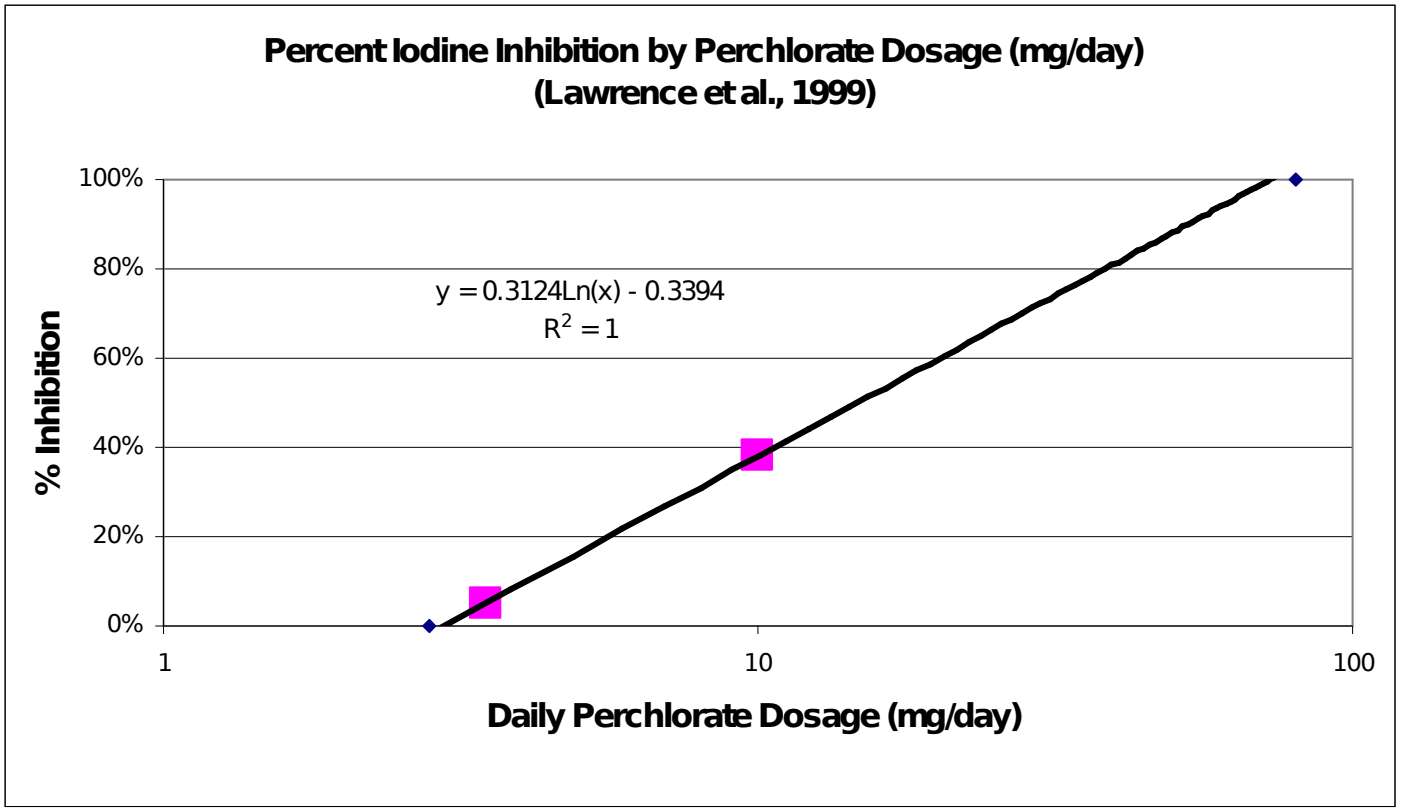
10 mg perchlorate daily in drinking water (n = 9)

	Baseline	1 week	2 weeks	Post 2 weeks
Perchlorate				
Urine (mg/24 hr)	< 0.5	7.7	7.5	< 0.5
Serum (ug/ml)	0	0.61	0.59	0
TSH (ug/dl)	1.05	1.00	0.96	1.23
TFI	6.3	6.2	6.3	6.3
T4 (ug/dl)	6.6	6.7	6.6	6.5

Laboratory Exposure Study of Perchlorate in Water

	Exposure	Uptake Inhibition	p value
Observed			
	3.5 mg	10.0 %	(ns)
	10.8 mg	38.2 %	($p < 0.05$)
Predicted			
	1 mg	0.0 %	
	100 mg	100 %	

Laboratory Exposure Study of Perchlorate in Water

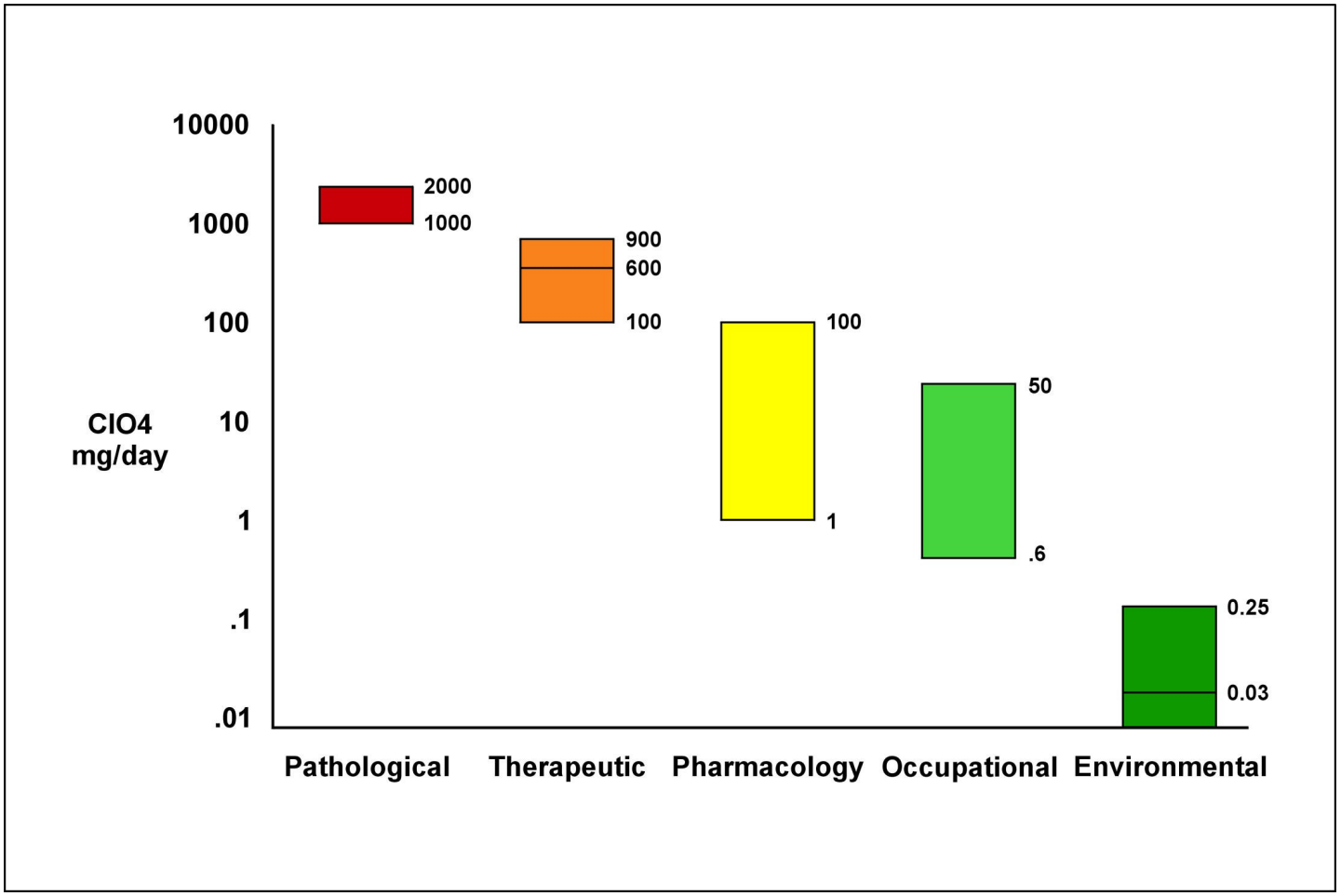


Thus, pharmacologically effective range is >1 – 100 mg/day.

Summary

1. Frank (Fatal) Effect Level	1,000 – 2,000 mg/day
Bone Marrow	15-30 mg/kg/day
2. Adverse Effect Level	100 – 1,000 mg/day
Thyroid	1.4- 14 mg/kg/day
3. Pharmacological Effect Level	**1 – 100 mg/day**
Iodine Metabolism	**0.014-0.14 mg/kg/day**
4. Occupational Level	1 – 50 mg/day
No hormone effect	0.014-0.10 mg/kg/day
5. Environmental Level	10- 250 µg/day
No hormone effect	0.00014-0.00057 mg/kg/day

Human Health and Perchlorate Exposure Ranges



Acknowledgements

- Martha Doemland, PhD
- Zili Li, MD, MPH
- Feng Xiao Li, MD, PhD
- Dan Byrd, PhD
- Gloria Deyhle, RN
- David Sesser, BA
- Michael Skeels, PhD, MPH
- Arnold Engel, MD
- Lisa Mims, MPA
- James Howgate, MPH
- Leslie Butler, MPH